REMARKS

This document is submitted in reply to the office action dated September 7, 2007 ("Office Action").

Applicants have amended claims 1 and 20 to more particularly and distinctively point out the subject matter that they deem as their invention. Further, Applicants have rewritten claim 11 in independent form. No new matter has been introduced.

Claims 1, 8-12, 20, and 22-25 are under examination. Applicants respectfully request that the Examiner reconsider this application in view of the following remarks.

Rejection under 35 U.S.C. § 112, First Paragraph (New Matter)

The Examiner rejects claims 1, 6-12, 20, and 22-25 for containing new matter. See the Office Action, pages 34, section 3. More specifically, he asserts that the specification has no support for the term "Mongoloid or a Mongoloid descendent" recited in independent claims 1 and 20. Note that this term was added to claims 1 and 20 in Applicants' reply co-filed with the Request for Continued Examination. Applicants have removed the term at issue from both claims 1 and 20, rendering this rejection moot.

Rejection under 35 U.S.C. § 112, First Paragraph (Enablement)

Applicants address separately below certain previously asserted grounds for rejection as applied to currently amended claim 1, as well as the grounds for rejection raised in the instant Office Action.

I

Applicants would like to bring to the Examiner's attention that currently amended claim 1 is substantially identical to previously presented claim 1 shown in Applicants' replies dated September 18, 2006 and March 19, 2007. Both currently amended claim 1 and previously presented claim 1 cover a method of assessing a human patient's risk for developing carbamazepine (CBZ)-induced Steven-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) by determining the presence of HLA-B*1502 in that patient.

In both the Final Office Action dated December 18, 2006 and the Advisory Action dated April 23, 2007, the Examiner rejected previously presented claim 1 for lack

of enablement. See the Final Office Action, pages 3-9; and the Advisory Action, page 2. The Examiner asserted that the method of claim 1 was not applicable to Caucasian patients, as Caucasia SJS/TEN patients did not carry HLA-B*1502 according to Affirevic et al. and Lonjou et al. See the Final Office Action, page 6, last paragraph; and page 11, second paragraph through page 12, first paragraph. The Examiner further contended that Applicants failed to provide evidence of any causal relationship between the presence of HLA-B*1502 and the development of CBZ-induced SJS/TEN. See the Advisory Action, page 2. Of note, currently amended claim 1 covers a method essentially the same as that covered by previously presented claim 1. Thus, the Examiner's grounds for rejection are applicable to currently amended claim 1. Applicants address below these grounds as applied to currently amended claim 1.

The Examiner challenged the proposition that HLA-B*1502 plays an essential role in the pathogenesis of CBZ-induced SJS/TEN development. Applicants herewith submit Dr. Yuan-Tsong Chen's declaration ("Declaration") to present experimental data demonstrating that HLA-B*1502 is directly involved in the development of CBZ-induced SJS/TEN.

The Declaration points out that cytotoxic T cells are effector cells in CBZ-induced SJS/TEN. Namely, they trigger apoptosis of keratinocytes and release of cytokines, leading to erosions of skin and mucous membranes. See Exhibits A and B attached to the Declaration. Figure 1 in the Declaration shows that CBZ-specific T cells isolated from SJS/TEN patients (carrying HLA-B*1502) are restricted to HLA-B*1502. In other words, CBZ is presented on HLA-B*1502 to activate CBZ-specific T cells. Further, Figure 2 in the Declaration indicates that the CBZ-activated T cells are cytotoxic against cells that present CBZ via HLA-B*1502. Taken together, these data demonstrate that HLA-B*1502 presents CBZ to CBZ-specific T cells, thereby activating them to become cytotoxic T cells (effector cells in CBZ-induced SJS/TEN). Accordingly, a skilled person in the art would readily know that HLA-B*1502 is directly involved in the development of CBZ-induced SJS/TEN. Thus, he or she would also know that any HLA-B*1502 carrier, regardless of his or her ethnic background, is at risk for developing CBZ-induced

SJS/TEN. In other words, the method of currently amended claim 1, i.e., assessing a human patient's risk for developing CBZ-induced SJS/TEN based on the presence of HLA-B*1502 in that patient, is applicable to patients of any ethnic background, including Caucasians.

In view of the above remarks, Applicants submit that currently amended claim 1 is enabled as applied to any human patient, including a Caucasian patient.

II

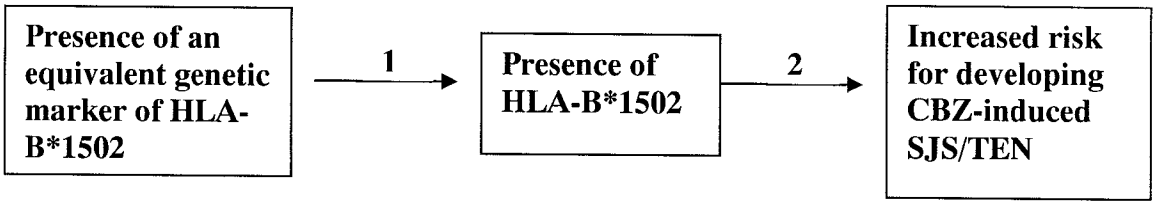
Applicants now traverse the enablement rejection of claims 1, 8-12, and 22 asserted in the present Office Action. The Examiner raises three grounds for rejection, which are addressed separately below.

First, the Examiner asserts that the specification does not enable associating the presence of HLA-B*1502 with "a risk for developing CBZ-induced SJS/TEN" recited in claim 1, as it only teaches that the presence of this HLA allele indicates an increased risk of developing the disease. See the Office Action, page 8, first paragraph. Applicants have amended claim 1 to replace "a risk" with "an increased risk," rendering this ground for rejection moot. Since the Examiner does not assert other grounds for rejecting claims 8-10, all of which depend from claim 1, Applicants submit that, for the same reasons, this amendment also overcomes the rejection of these claims.

Second, referring to claim 11, the Examiner holds the position that the specification is not enabling for a method of using any equivalent genetic marker of HLA-B*1502, e.g., Cw*0801, to predict a risk for developing CBZ-induced SJS/TEN. See the Office Action, page 6, first paragraph. More specifically, the Examiner asserts that the specification fails to provide: (i) "any statistical analysis of the association of HLA-Cw*0801 with carbamazepine-induced SJS/TEN, and (ii) "any analysis of linkage between HLA-B*1502 and HLA-Cw*0801." See the Office Action, page 8, second paragraph. Applicants respectfully disagree.

Claim 11, now rewritten in independent form, covers a method of assessing a human patient's risk for developing CBZ-induced SJS/TEN by determining the presence of an equivalent genetic marker of HLA-B*1502 (e.g., HLA-Cw*0801). The presence of

the equivalent genetic marker is indicative of the presence of HLA-B*1502, which in turn is indicative of an increased risk for developing the disease. To facilitate discussion, Applicants provide the following chart to show the basis of this claimed method:



This chart indicates that the method of claim 11 requires two pieces of knowledge: (1) linkage between HLA-Cw*0801 and HLA-B*1502, i.e., presence of the latter indicative of presence of the former, and (2) association between HLA-B*1502 and a risk for developing SJS/TEN, i.e., presence of this HLA allele indicative of an increased risk for developing the disease.

Knowledge (1) exists in the pertinent art. For example, the linkage between HLA-B*1502 and HLA-Cw*0801 is described in Exhibits 1 and 2 submitted with Applicants' Reply dated March 19, 2007. According to MPEP § 2163, "[w]hat is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." Applicants thus submit that there is no need to provide the well-known linkage between HLA-B*1502 and its equivalent genetic markers, e.g., HLA-Cw*0801, in the present application, as required by the Examiner.

Knowledge (2) is well established in the present specification, as acknowledged by the Examiner. See the Office Action, page 5, first paragraph.

Equipped with the two pieces of knowledge, a skilled person in the art would readily know that the presence of an equivalent genetic marker (e.g., HLA-Cw*0801) indicates the presence of HLA-B*1502, which in turn indicates an increased risk for developing the disease. Thus, the association between HLA-Cw*0801 and a risk for developing the disease has been established. Accordingly, there is no need to provide "any statistical analysis," as required by the Examiner, to show this already-established association.

In view of the above remarks, Applicants submit that the specification, combined with knowledge in the art, enables the method of claim 11. The Examiner rejects claim 12, dependent from claim 11, on the same ground. For the same reasons, claim 12 is also enabled.

Finally, referring to claim 22, the Examiner asserts that the specification does not enable pharmacogenomic profiling of a human patient by determining in the patient the presence of thiopurine methyltransferase or genes associated with long-QT syndrome. See the Office Action, page 5, first paragraph.

Claim 22, dependent from claim 20, covers a method of pharmacogenomics profiling for a human patient by determining the presence of HLA-B*1502, which indicates predisposition of CBZ-induced SJS/TEN, and by further determining at least one genetic factor of thiopurine methyltransferase and the genes for the long-QT syndrome.

It is the Examiner's position that this claim "require[s] knowledge of an association between thiopurine methyltransferase or long-QT syndrome and predisposition of an individual to develop SJS or TEN in response to a carbamazepine." See the Office Action, page 6, third paragraph. Applicants respectfully disagree.

The specification teaches that

> "[t]he method [pharmacogenomic profiling] can optionally comprise the determination of other genetic factors. Those other genetic factors may be associated with the predisposition for any disease or medical condition, including adverse drug reactions. For example, these other genetic factors may be selected from the group consisting of thiopurine methyltransferase and the genes for the long-QT syndrome." See page 7, paragraph [0037], lines 5-10.

In other words, "thiopurine methyltransferase" recited in claim 22 is a genetic factor associated with a disease, which does not need to be CBZ-induced SJS/TEN, and "the genes for long-QT syndrome," also recited in this claim, are risk factors for the predisposition of long-QT syndrome. Clearly, the Examiner misunderstands "thiopurine methyltransferase" and "the genes for long-QT syndrome" as being associated with a risk

for developing CBZ-induced SJS/TEN. Applicants thus submit that the Examiner's ground for rejection, based on a misunderstanding of fact, is invalid.

III

For the reasons set forth above, Applicants respectfully request that the Examiner withdraw the enablement rejection.

CONCLUSION

It is believed that all of the pending claims have been addressed. However, the absence of a reply to a specific rejection, issue or comment does not signify agreement with or concession of that rejection, issue or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper, and the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

No fee is believed to be due. Please apply any other charges or credits to Deposit Account No. 50-4189, referencing Attorney Docket No. 70003-003001.

Respectfully submitted,

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